Kaohsiung Journal of Medical Sciences (2013) 29, 547–553

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

Judging disease activity in rheumatoid arthritis by serum free kappa and lambda light chain levels

Yun Ye [a], Su-Liang Li [a], Ming Xie [b], Ping Jiang [a], Kai-Ge Liu [a], Ya-Jun Li [a,*]

[a] *Department of Clinical Laboratory, The First Affiliated Hospital of Xi'an Medical University, Xi'an, Shaanxi, China*
[b] *Department of Pathogenic Microbiology and Immunology, Medical School of Xi'an Jiaotong University, Xi'an, Shaanxi, China*

Received 22 March 2012; accepted 21 September 2012
Available online 14 June 2013

KEYWORDS
Disease activity;
Disease activity score;
Light chain;
Rheumatoid arthritis

Abstract The study aimed to evaluate the levels of serum free kappa (κ) and lambda (λ) light chains in patients with rheumatoid arthritis (RA) as well as exploring the association between serum free κ and λ light chains and activity of RA. For this purpose, healthy individuals and patients with active RA and RA in remission were enrolled, and their serum levels of free κ and λ light chains were measured using rate nephelometry. The diagnostic accuracy of serum free κ and λ light chains was evaluated by receiver operating characteristic curves and 95% confidence intervals for areas under the curve (AUC). The results obtained indicated that the levels of serum free κ and λ light chains in patients with active RA were significantly higher than those of patients in remission and of healthy controls ($p < 0.05$). Further, the AUC values in patients with active RA were 0.871 for free κ light chain and 0.781 for free λ light chain. When the optimal cut-off point for serum κ light chain was 8.02 g/L, the maximum sensitivity and specificity were 82.5% and 82.5%, respectively, and when the optimal cut-off point for serum λ light chain was 3.57 g/L, the maximum sensitivity and specificity were 80% and 82.5%, respectively. It was thus found that serum levels of free κ and λ light chains were positively correlated with disease activity in RA, the Disease Activity Score 28 (DAS28), and values for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet count (PLT), rheumatoid factor (RF), and anticitrullinated protein antibody (ACPA) ($p < 0.05$). In conclusion, high serum levels of free κ and λ light chains in patients with active RA are closely correlated with disease activity parameters including DAS28, CRP, ESR, PLT, RF, and ACPA. Thus, the above-mentioned levels of serum free κ and λ light chains may be used as important indicators of activity of RA.

* Corresponding author. Department of Clinical Laboratory, The First Affiliated Hospital of Xi'an Medical University, No. 48, West Fenghao Road, Xi'an, Shaanxi 710077, China.
E-mail address: yeyun236@163.com (Y.-J. Li).

http://dx.doi.org/10.1016/j.kjms.2013.01.013

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs. However, it principally attacks the synovial joints [1]. The process produces an inflammatory response in the synovium (synovitis) secondary to hyperplasia of the synovial cells as well as excess synovial fluid. Further, it also leads to the development of pannus in the synovium. The pathology of the disease process often leads to destruction of the articular cartilage and ankylosis of the joints [2]. RA can also produce diffuse inflammation in the lungs, pericardium, pleura, and sclera, as well as nodular lesions, most common in the subcutaneous tissue under the skin [3].

Although the cause of RA is unknown, autoimmunity plays a pivotal role in both its chronicity and progression. Hence, RA is considered to be a systemic autoimmune disease. Infectious agents such as viruses, bacteria, and fungi have long been suspected as potential causes of RA, but none has been proven as the cause. Infections may trigger activation of the immune system in susceptible individuals, thereby leading to immune system disorders. Further, cytokines are important in the pathologic procession of the rheumatoid synovial lesion [4].

B cells are precursor cells that produce RA antibodies and also play an important role in modulation of the immune response. B cells are involved in the inflammatory reaction and act as a bridge between the specific and nonspecific immune responses [5]. Further, B cells migrate to the synovial membrane in response to cytokine and B cell receptor (BCR). The increase in the quantity of some cytokines can further activate the B cells. It has been observed that the number of plasma cells in patients with RA can maintain a steady growth for several months, which indicates that the chronic inflammation in the infected joints corresponds with the persistent activation of the B cells [6].

Immunoglobulin consists of light chains and heavy chains. The light chains include κ and λ types. Normal serum could be the place to reserve the light chain, including some free light chain. With overexpression of key genes involved in modulation of the immune response, dysfunction of the T- and B-lymphocytes is induced, with cloning secretion from the plasma cell is increased, thereby leading to the production of plenty of antibodies and free κ and λ light chains [7]. Thus, the levels of free κ and λ light chains could reflect B cell activation as well as being related to the progress of RA.

The serum κ and λ light chains are the focus of the present experiment, in which 40 patients with RA in remission and 40 patients with active disease were selected. Analysis of correlation with the activity of RA indicates that serum immunoglobulin κ and λ light chains could be used as biomarkers for diagnosing the active period of RA.

Materials and methods

Patients

In the present study, 80 patients with RA were successively selected—one from every two inpatients and outpatients at the affiliated Hospital of Xi'an Medical College from January 2008 to January 2010. This selection was made in accordance with the 1987 American College of Rheumatology (ACR) classification criteria for RA [8]. The study protocol was approved by the ethics committee at the institution. All patients and healthy controls provided written informed consent.

Assessment of RA disease activity

According to the 1990 Disease Activity Score 28 (DAS28) [9,10], higher scores along a range of 1 to 10 points suggest higher disease activity. Calculations are made as follows:

(1) Tender joint count. Check 28 joints including the proximal interphalangeal joints, metacarpophalangeal joints, wrist, elbow, shoulder, and knee joints, and then calculate the number of tender joints in the state of joint tenderness or passive activity (T28).
(2) Swollen joint count. Check 28 joints as above and then calculate the number of swollen joints (Sw28).
(3) Then apply the following equation: $\mathrm{DAS28} = [0.56 \times \mathrm{sqrt(T28)} + 0.28 \times \mathrm{sqrt(SW28)} + 0.70 \times \mathrm{Ln(ESR)}] \times 1.08 + 0.16$, where ESR is erythrocyte sedimentation rate).

Case groups

The patients were divided into two groups—those with active disease and those in remission—in accordance with the 1987 ACR classification criteria for RA. Forty patients (10 male and female 30) with active RA were not being treated with disease-modifying antirheumatic drugs. These patients had an age range of 18—65 years, with a mean age of 49 $\pm$ 13 years, and a disease duration of 2 months to 16 years. In addition, 40 patients (12 male and 28 female) with RA in remission were being treated with nonsteroidal anti-inflammatory drugs, methotrexate, leflunomide, or hydroxychloroquine. These patients had an age range of 19—68 years, with a mean age of 47 $\pm$ 11 years, and a disease duration of 6 months to 20 years. Comparisons were made between the active and remission phases of RA. The results demonstrate that the indicators of age, gender, and disease duration were of no statistical significance.

Patients with other rheumatic diseases or heart, brain, liver, kidney, hematopoietic system, and other serious diseases were excluded. A total of 40 blood donors (14 male and 26 female) were selected as the healthy control group by conducting a physical examination at the affiliated Hospital of Xi'an Medical College. These donors had an age range of 20—62 years, mean 43 $\pm$ 11 years, and their age and gender were matched with participants in the case group.

Clinical and laboratory parameters

The duration of morning stiffness, tender joint count, swollen joint count, and values for C-reactive protein (CRP), ESR, platelet count (PLT), anticitrullinated protein antibody (ACPA), and rheumatoid factor (RF) were selected as the parameters for researching test cases in clinical as well as laboratory conditions. Applying the principles of rate nephelometry, serum free κ and λ chains were measured using a BN ProSpec (Dade Behring Inc, USA) automatic special protein analyzer.

Statistical analysis

Statistical analyses were performed with SPSS 11.5 software (IBM SPSS Statistic, USA). The descriptive results of continuous variables (age, body mass index, and duration of morning stiffness) followed a normal distribution and were presented as $\overline{X} \pm s$. Comparisons between the two groups were made using the paired-samples t test, while comparisons among the three groups were made using one-way analysis of variance. ESR, CRP, RF, ACPA, and κ and λ values followed a skewed distribution and were presented as medians, and the statistical significance for intergroup differences was assessed using the Kruskal–Wallis test; pairwise comparison was carried out with the Mann–Whitney U test. Nonparametric material was assessed with the Pearson Chi-square test. Spearman correlation analysis was used for assessing the relationship between the serum free κ and λ light chains and other variables, with p values <0.05 considered statistically significant.

Using the ACR classification standard as the gold standard, serum free κ and λ light chains and the sensitivity, specificity, positive predictive value, negative predictive value, the positive likelihood ratio, the negative likelihood ratio, and Youden index (the diagnostic index for the active period of RA) were compared. Receiver operator curves (ROC) curves were drawn to determine the best fit for each index critical value, and the area under the curve (AUC) and 95% confidence interval (CI) were used to express the overall efficiency of diagnosis.

Results

Related parameters in active RA and in remission

It was found that the differences in age, weight, and gender between the three groups were not statistically significant ($F = 0.843$ and 1.081 for age and weight respectively; Chi-square $= 0.012$; for gender; $p > 0.05$). The duration of morning stiffness and DAS28 scores in the active phase were significantly higher than those in patients in remission ($t = 25.594$ and 20.163, respectively; $p < 0.01$).

Statistical significance for the intergroup differences was assessed by the Kruskal–Wallis test. The related parameters of the RA patients with active disease, including ESR, CRP, PLT, RF, and ACPA, were found to be significantly higher than those in healthy controls and patients with RA in remission ($H = 101.193$, 60.902, 90.947, 100.856, and 106.032, respectively; $p < 0.01$).

Pairwise comparison was carried out using the Mann–Whitney U test. Levels of the above-mentioned parameters were higher in the active phase than in patients in remission or healthy controls (active phase compared with remission, $Z = -7.251$, -5.120, -7.541, -6.341, and -5.709 for ESR, CRP, PLT, RF, and ACPA, respectively; active phase compared with the healthy controls, $Z = -7.704$, -6.408, -7.701, -5.703, and -7.718, respectively; remission compared with healthy controls, $Z = -6.752$, -3.264, -5.295, -7.633, -7.723, respectively; $p < 0.05$) (Table 1).

Levels of serum free κ and λ light chains from different disease phases

Statistical significance for the intergroup differences was assessed by the Kruskal–Wallis test. The serum levels of free κ and λ light chains in each group showed significant differences ($H = 88.837$ and 87.572, respectively; $p < 0.05$).

Pairwise comparison was carried out using the Mann–Whitney U test. The levels of serum free κ and λ chains in patients with active RA were found to be significantly higher than in those in remission and healthy controls (active phase compared with remission, $Z = -5.090$ and -5.856, respectively; active phase compared with healthy controls, $Z = -7.410$ and -7.574, respectively; remission compared with healthy controls, $Z = -7.068$ and -7.237, respectively; $p < 0.05$). However, the ratios of κ:λ were

Table 1 Comparison of baseline demographics and clinical and laboratory data from patients with active rheumatoid arthritis, patients in remission, and healthy controls.

Characteristics	Active phase ($n = 40$)	Remission ($n = 40$)	Controls ($n = 40$)	Statistics	p
Age (yr)	$49 \pm 13^{\#}$	$47 \pm 11^{\#}$	$43 \pm 11^{\#}$	$F = 0.843$	0.68
Female (n)	10	12	14	Chi-square $= 0.012$	0.91
Body mass index (kg/m^2)	$24.63 \pm 3.7^{\#}$	$23.7 \pm 3.8^{\#}$	$23.7 \pm 3.8^{\#}$	$F = 1.081$	0.37
Duration of morning stiffness (min)	$61 \pm 11^{a,\#}$	$10 \pm 4^{\#}$	0	$t = 25.594$	<0.01
ESR (mm/h)	53 (22–109)^{a,b,*}	18 (10–26)^{c,*}	5 (2–10)*	$H = 101.193$	<0.01
CRP (mg/L)	26.6 (3.3–60.0)^{a,b,*}	3.6 (0.56–4.8)^{c,*}	0.85 (0.28–2.6)*	$H = 60.902$	<0.01
PLT (10^9/L)	363 (257–442)^{a,b,*}	209 (176–278)^{c,*}	155 (116–180)*	$H = 90.947$	<0.01
RF (kIU/L)	96.7 (35.5–182)^{a,b,*}	28.5 (10.3–36.8)^{c,*}	5.2 (3.5–14.6)*	$H = 100.856$	<0.01
ACPA (kIU/L)	53.5 (35.6–481)^{a,b,*}	20.9 (13.4–28.6)^{c,*}	3.6 (2.2–7.6)*	$H = 106.032$	<0.01
DAS28	$7.6 \pm 1.5^{a,\#}$	$1.6 \pm 0.3^{\#}$	0	$t = 20.163$	<0.01

ACPA = anticitrullinated protein antibody; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; PLT = platelet count; RF = rheumatoid factor. # means ± standard deviations; * medians (ranges).

[a] $p < 0.05$, active phase vs. remission.

[b] $p < 0.05$ active phase vs. controls.

[c] $p < 0.05$ remission vs. controls.

Table 2 Serum free κ and λ chain levels and κ:λ ratio in patients with active rheumatoid arthritis, patients in remission, and healthy controls.

Variable	Active phase ($n = 40$)*	Remission ($n = 40$)*	Controls ($n = 40$)*	H	p
κ (g/L)	9.83 (2.98–11.84)[a,b]	4.15 (2.15–10.32)[c]	2.77 (1.68–3.64)	88.84	0.01
λ (g/L)	5.38 (1.71–6.38)[a,b]	2.27 (1.41–5.51)[c]	1.53 (0.98–2.10)	87.57	0.01
κ:λ ratio	1.65 (1.49–2.38)	1.68 (1.51–2.42)	1.63 (1.53–2.45)	0.362	0.697

* medians (ranges).
[a] $p < 0.05$, active phase vs. remission.
[b] $p < 0.05$ active phase vs. controls.
[c] $p < 0.05$ remission vs. controls.

considered not statistically significant ($H = 0.362$, $p = 0.696$) (Table 2 and Figs. 1 and 2).

Diagnostic accuracy of serum free κ and λ light chains in active disease

The ROC curves for evaluating the diagnostic efficiency of serum κ and λ light chains demonstrated that the AUCs in patients with active RA were 0.871 (95% CI 0.785–0.956) for free κ light chain and 0.781 (95% CI 0.667–0.896) for λ light chain. Further, when the optimal cut-off points determined by the ROC curves for serum κ and λ were 8.02 g/L and 3.57 g/L, respectively, the maximum sensitivity and specificity were 82.5% (33/40) and 82.5% (33/40) for free κ light chain, and 80% (32/40) and 82.5% (33/40) for free λ light chain. In the present study, the ROC curves were also used for predicting other parameters including positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, accuracy, and AUC (95% CI). These values are listed in Table 3 (see also Fig. 3).

Correlation between serum free κ and λ light chains and other parameters in active RA

Linear correlation analysis was carried out to evaluate the relationship between serum free κ (g/l) and λ (g/l) light chains and DAS28 (score), CRP (mg/l), ESR (mm/h), PLT (10^9/l), RF (KIU/l), and ACPA (KIU/l) values. The results demonstrate that the above parameters were positively correlated with serum free κ light chain ($r = 0.774$, 0.693, 0.729, 0.682, 0.348, and 0.316, respectively; $p < 0.05$) and λ light chain ($r = 0.665$, 0.634, 0.694, 0.658, 0.362, 0.434, respectively; $p < 0.05$) (Fig. 4 and Table 4).

Discussion

RA is the most common inflammatory joint disease and significantly affects patients' quality of life. In time, it also leads to a substantial loss of joint functionality [11]. The main feature of RA is hyperplasia of the synovial cells, which leads to the formation of an invasive pannus. Pannus expansion can promote the destruction of cartilage and bone, thereby resulting in a loss of joint functionality [12].

The immunoglobulin light chains are the κ and λ types. Normally, the light chains exist in two sections, one section being stored in the plasmocytes. In general, the resultant production speed of the light chain is 8 minutes greater than that of the heavy chain. Thus, after the formation of one monomolecule of the immunoglobulin, an excess of light chain exists. The pool of free light chain in the plasma cells is called the light chain library [13]. The newly synthesized light chain appears in the light chain library, thereby replacing the reserved light chain and assembling into new immunoglobulin. Therefore, the normal serum acts as another reserve and a certain amount of polyclonal light chain is always available [14].

In autoimmune diseases, the overexpression of key genes involved in regulation of the immune response cause dysfunction of the T- and B-lymphocytes, along with increased cloning secretion of the plasma cells and

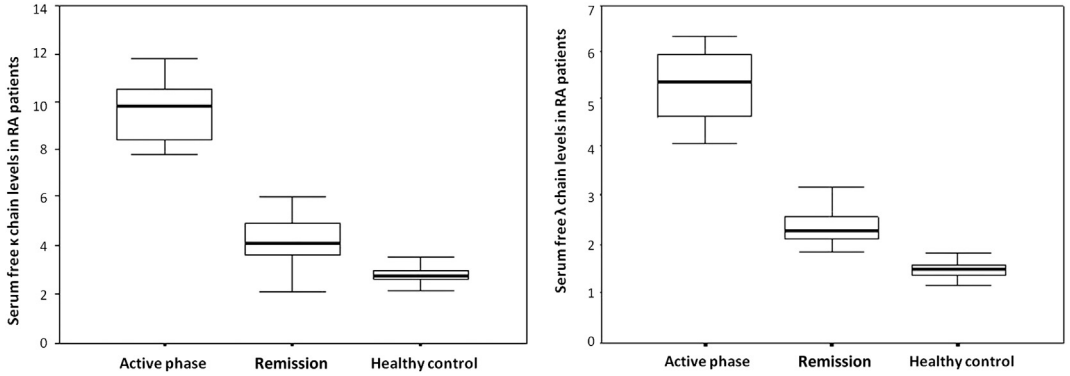

Figure 1. Serum levels of free κ and λ chain (g/L) in patients with active rheumatoid arthritis (RA), patients in remission, and healthy controls.

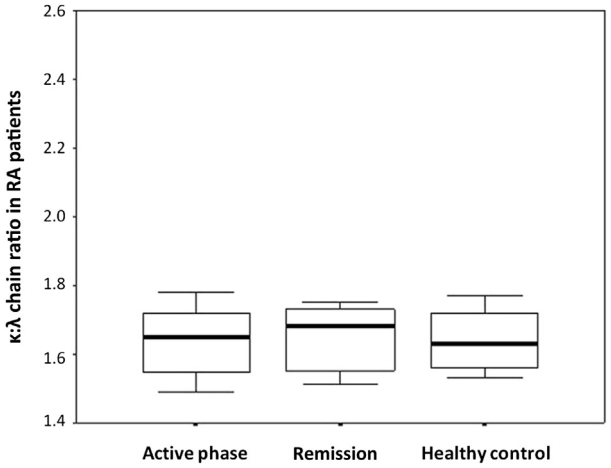

Figure 2. The κ:λ chain ratio in patients with active rheumatoid arthritis (RA), patients in remission, and healthy controls.

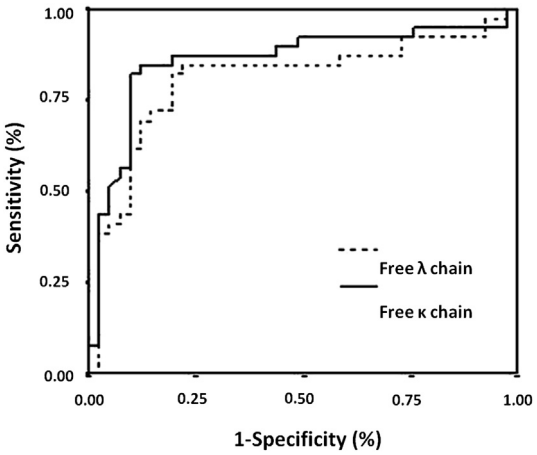

Figure 3. Receiver operator curves of diagnostic parameters for active rheumatoid arthritis. When the optimal cut-off point for serum κ light chain was 8.02 g/L, the maximum sensitivity and specificity were 82.5% and 82.5%, respectively (area under the curve 0.871, $p < 0.01$). However, when the optimal cut-off point for serum λ light chain was 3.57 g/L, the maximum sensitivity and specificity were 80% and 82.5%, respectively (area under the curve 0.781, $p < 0.01$).

increased immunoglobulin production. Further, the level of κ and λ light chains in the serum increases relatively [15,16]. Moyes et al. [17] established that the CDR3 of the κ and λ light chain genes in the synovial membrane was longer, and they overexpressed in the inflammatory. Thus, the increase in level of light chains is one of the crucial factors in the pathologic progression of RA. In addition, Gottenberg et al. [18] found that levels of the κ and λ light chains had a strong relationship to activation of the B cells, showing a positive correlation with B cell activation.

The activity of RA indicates the speed of development of the illness. Thus, an evaluation of disease activity and progression can successfully guide treatment of the disease. DAS28 is an evaluation criterion that is based on the number of swollen joints and on experimental indexes. These factors present an objective assessment of disease activity. In the late 1990s, research conducted in Italy [19] confirmed that DAS28 is the best standard for defining the activity of RA. At present, clinicians have combined DAS28 scores with CRP, ESR, ACPA, RF, and PLT values for judging disease activity in RA [20,21]. Through an analysis of the correlation between the serum free κ and λ light chains and the activity index of RA, the present study confirmed that

Table 3 Comparison of the diagnostic efficiency of serum free κ and λ light chains with other diagnostic parameters in patients with active rheumatoid arthritis (RA).

Variable	Optimal cut-off point	Diagnostic efficiency of parameters in patients with RA								AUC (95% CI)
		Specificity (%)	Sensitivity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio	Youden Index	Accuracy (%)	
κ (g/l)	8.02	82.5	82.5	82.5	82.5	4.71	0.21	0.65	82.5	0.871 (0.785—0.956)
λ (g/l)	3.57	82.5	80	82.5	80	4.49	0.24	0.63	81.3	0.781 (0.737—0.926)
DAS28 (score)	3.30	87.5	90	87.8	87.7	7.2	0.11	0.77	90.4	0.932 (0.894—0.991)
ACPA (KIU/l)	33.5	85	80.5	88.9	81.3	4.36	0.18	0.66	82.8	0.851 (0.792—0.957)
CRP (mg/l)	25.1	70	70	70	72.5	2.45	0.39	0.40	71.3	0.763 (0.707—0.892)
ESR (mm/h)	45	57.5	65	65	57.5	1.60	0.64	0.23	61.3	0.615 (0.516—0.753)
PLT (10^9/l)	319	60	60	60	65	1.66	0.59	0.20	62.5	0.623 (0.522—0.767)
RF (KIU/l)	60	57.5	67.5	67.5	57.5	1.70	0.58	0.25	62.5	0.581 (0.473—0.725)

ACPA = anticitrullinated protein antibody; AUC = area under the curve; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; PLT = platelet count; RF = rheumatoid factor.

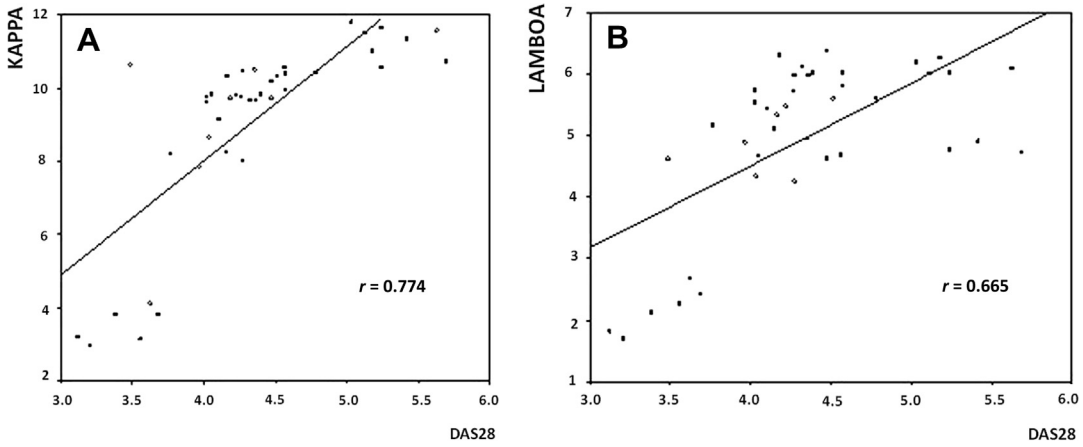

Figure 4. Analysis of correlation between serum free κ (A) and λ (B) light chains and Disease Activity Score 28 (DAS28). Linear correlation analysis shows that serum free κ and λ light chain levels were positively correlated with DAS28 score in patients with active rheumatoid arthritis ($r = 0.774$ and 0.665, respectively; $p < 0.05$).

serum levels of free κ and λ light chains increased in close relation to the disease activity index ($p < 0.05$).

In the present study, it was observed that the serum levels of κ and λ light chains in normal controls were low, while levels in patients were significantly higher. Levels of serum κ and λ light chains were particularly elevated in the active phase of RA ($p < 0.05$). However, the difference in the κ:λ ratio between the groups was not statistically significant. The results obtained indicated that RA is a polyclonal proliferation disease. According to the ROC curve of the serum κ and λ light chains, it was observed that the AUC of serum κ and λ light chains used to diagnose RA was 0.871 and 0.781, respectively. When the κ light chain level was 8.02 g/L, the diagnostic sensitivity for active RA was 82.5% and the specificity was 82.5%; when the λ light chain level was 3.57 g/L, the diagnostic sensitivity for active RA was 80% and the specificity 82.5%. Linear correlation analysis was used to evaluate the relationship between the serum free κ and λ light chains and DAS28, CRP, ESR, PLT, RA, and ACPA values. The results demonstrated that serum free κ and λ light chain levels were positively correlated with the above parameters. The analysis of the relevance of serum free κ and λ light chains for activity of RA indicates that serum free κ and λ light chains values combined with DAS28, CRP, and ESR could be used for the early diagnosis of active RA. Thus, serum free κ and λ light chains can be used as a simple and fast experimental index in the differential diagnosis of disease activity and paracmasia in RA patients.

In conclusion, the results obtained demonstrated that the serum κ and λ light chains are important inflammatory indexes and may be used as indicators of disease activity in RA.

Table 4 Analysis of correlation between serum free κ and λ light chains and other parameters for patients with active rheumatoid arthritis.

Variable	Serum free κ chains		Serum free λ chains	
	r	*p*	*r*	*p*
DAS28	0.774	0.01	0.665	0.01
CRP (mg/L)	0.693	0.01	0.634	0.01
ACPA (kIU/L)	0.729	0.01	0.694	0.01
ESR (mm/h)	0.682	0.01	0.658	0.01
PLT (10^9/L)	0.348	0.028	0.362	0.02
RF (kIU/L)	0.316	0.047	0.434	0.036

ACPA = anticitrullinated protein antibody; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; PLT = platelet count; RF = rheumatoid factor.

Acknowledgments

This study was supported by funds from the Education Department of Shaanxi Provincial Government (11JK0723) and the Xi'an Medical University (11F208).The authors express gratitude to the study participants and research personnel for their involvement in the study. The authors would also like to thank Dr Kai Wen and Dr Yang Ji for their valuable assistance.

References

[1] Komatsu N, Takayanagi H. Inflammation and bone destruction in arthritis: synergistic activity of immune and mesenchymal cells in joints. Front Immunol 2012;3:77.
[2] Jacob J, Sartoris D, Kursunoglu S, Pate D, Pineda CJ, Braun RM, et al. Distal interphalangeal joint involvement in rheumatoid arthritis. Arthritis Rheum 1986;29:10—5.
[3] Mottonen TT. Prediction of erosiveness and rate of development of new erosions in early rheumatoid arthritis. Ann Rheum Dis 1988;47:648—53.
[4] Clavel G, Bessis N, Boissier MC. Recent data on the role for angiogenesis in rheumatoid arthritis. Joint Bone Spine 2003; 70:321—6.
[5] Dorner T, Burmester GR. The role of B cells in rheumatoid arthritis: mechanisms and therapeutic targets. Curr Opin Rheumatol 2003;15:246—51.
[6] Lindenau S, Scholze S, Odendahl M, Dörner T, Radbruch A, Burmester GR, et al. Aberrant activation of B cells in patients with rheumatoid arthritis. Ann N Y Acad Sci 2003;98:246—8.
[7] Shi GY. Arthritis overview. Beijing: China Medical Science Press; 2005.

[8] Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315—24.
[9] Vander Cruyssen B, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, et al. DAS28 best reflects the physician's clinical judgement of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. Arthritis Res Ther 2005; 7:1063—71.
[10] van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990; 49:916—20.
[11] Khurana R, Berney SM. Clinical aspects of rheumatoid arthritis. Pathophysiology 2005;12:153—65.
[12] Firestein GS, Zvaifler NJ. How important are T cells in chronic rheumatoid synovitis? II. T cell-independent mechanisms from beginning to end. Arthritis Rheum 2002;46:298—308.
[13] Nelson M, Brown RD, Gibson J, Joshua DE. Measurement of free kappa and lambda chains in serum and the significance of their ratio in patients with multiple myeloma. Br J Haematol 1992;81:223—30.
[14] Cao XW, Ju BH, Song BH. Detection of free κ、λ light chain in human serum. Pract Clin Med 2004;5:13—4.
[15] Levy RA, Gharavi AE, Sammaritano LR, Habina L, Qamar T, Lockshin MD. Characteristics of IgG antiphospholipid antibodies in patients with systemic lupus erythematosus and syphilis. J Rheumatol 1990;17:1036—41.
[16] Demaison C, Ravirajan CT, Isenberg DA, Zouali M. Analysis of variable region genes encoding anti-Sm and anti-cardiolipin antibodies from a systemic lupus erythematosus patient. Immunology 1995;86:487—94.
[17] Moyes SP, Maini RN, Mageed RA. Differential use of immunoglobulin light chain genes and B lymphocyte expansion at sites of disease in rheumatoid arthritis (RA) compared with circulating B lymphocytes. Clin Exp Immunol 1998;113:276—88.
[18] Gottenberg JE, Aucouturier F, Goetz J, Sordet C, Jahn I, Busson M, et al. Serum immunoglobulin free light chain assessment in rheumatoid arthritis and primary Sjogren's syndrome. Ann Rheum Dis 2007;66:23—7.
[19] Salaffi F, Peroni M, Ferraccioli GF. Discriminating ability of composite indices for measuring disease activity in rheumatoid arthritis: a comparison of the Chronic Arthritis Systemic index, Disease Activity score and Thompson's Articular Index. Rheumatology 2000;39:90—6.
[20] Agrawal S, Misra R, Aggarwal A. Autoantibodies in rheumatoid arthritis: association with severity of disease in established RA. Clin Rheumatol 2007;26:201—4.
[21] Marasovic-Krstulovic D, Martinovic-Kaliterna D, Fabijanic D, Morovic-Vergles J. Are the anti-cyclic citrullinated peptide antibodies independent predictors of, myocardial involvement in patients with active rheumatoid arthritis? Rheumatology (Oxford) 2011;50:1505—12.